

## Original Research Article

# A Study of Medical and Surgical Treatment of Patients with Brucella Spondylodiscitis

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### Abstract

The aim of the study was to systematically evaluate the clinical, radiological and prognostic features of 11 patients with Brucella Vertebral Osteomyelitis (BVO) in line with the literature. Microbiological and radiological features of patients who were diagnosed with BVO in a tertiary care center between the dates January 2016 and January 2019 were classified, then compared. The data obtained were statistically evaluated. Alpha significance value was considered as  $P < 0.05$ . Clinical, radiological and prognostic features of the patients should be evaluated carefully. Patients with an accurate diagnosis should be treated in a multidisciplinary manner. The rational use of antibiotics should be respected during antimicrobial therapy. Surgical treatment should be provided immediately in the event of therapeutic failure.

**Keywords:** Anti-Brucella Coombs test, Brucella immunoglobulin, Brucellar vertebral osteomyelitis, Magnetic resonance image, Wright's seroagglutination.

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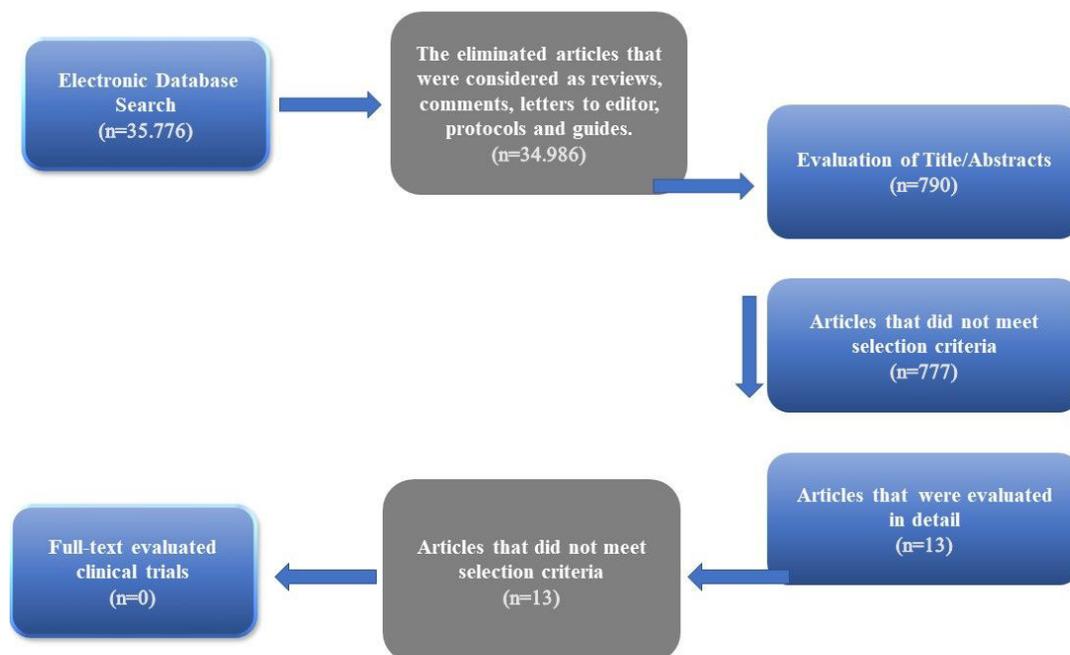
## INTRODUCTION

Vertebral osteomyelitis (VO), commonly known as spinal infection, remains an important clinical condition despite all the progress in diagnosis and treatment methods (Singh et al., 2018; von der Hoeh et al., 2018). Early diagnosis of VO is markedly difficult due to its sneaky and silent clinical course. The mean period elapsed until establishing a final diagnosis is approximately four months (Kamiya et al., 2018; Bianchini et al., 2018). Despite advances in both medical and invasive surgical modalities, no etiological diagnosis may always be made. Delayed diagnosis may cause complications such as neurological deficits or even loss of strength in the extremities. Spinal deformities may also occur following destructive lesions in some cases (Colmenero et al., 1997).

Many different microorganisms may cause VO. However, *Brucella Spp.* is one of the most common pathogens in patients with VO (Eren et al., 2014). *Brucella* species are small, Gram-negative, nonmotile,

non-spore-forming, rod-shaped (coccobacilli) bacteria. It is one of the most frequently isolated bacteria worldwide (Young et al., 2010).

Brucellosis is commonly accompanied by musculo-skeletal involvement. Particularly, vertebral column involvement is frequently observed. Brucellar vertebral osteomyelitis (BVO) most commonly affects the lumbar spine, it may also affect the thoracolumbar and lumbosacral junctions, isolated cervical and thoracic levels respectively. Patients with BVO may suffer from low back pain, which is abruptly starting and time-dependently increasing, along with other systemic symptoms. Patients may complain of difficulty in walking, myalgia and night pain. In the clinical examination, sensitivity in the affected vertebra is observed after direct palpation of the spinous process, and straight leg raise test result is positive. Waist movements may be restricted due to the pain. Spinal deformity is rarely seen, but it may be developed as a late complication when the diagnosis



**Figure 1.** Inclusion criteria and excluded studies.

is delayed (Ariza et al., 1985).

A multidisciplinary approach is essential in the management of spinal infections. Along with the clinical and microbiological findings, radiological examinations have increasing importance in the diagnosis and treatment of disease. The conventional radiological imaging findings have low sensitivity and specificity, and generally, provide limited support for the diagnosis of BVO. However, magnetic resonance image (MRI) has high sensitivity, and provide advantages in diagnosing BVO (Esmaeilnejad-Ganji et al., 2019).

It is of vital importance that BVO, which causes morbidity and mortality, should timely be diagnosed and that conservative or surgical treatment should be performed without delay. In this retrospective study, the aim was to evaluate clinical, radiological and prognostic features of 11 patients with BVO, which satisfied the inclusion criteria, out of 25 patients. In this way, it might be possible to evaluate the independent risk factors in patients having surgical treatment indication.

## MATERIALS and METHODS

In this retrospective study, the data used were retrieved from the archived medical records of patients after obtaining required legal approval from the directors of Namik Kemal University Training and Research Hospital. The target population of the study consisted of patients (n=25) diagnosed with VO between the dates January 2016 and January 2019. Adult patients (n=11) diagnosed with BVO were included in the study.

## Eligibility Criteria

According to the archived medical records, the patients were referred to the neurosurgery and infectious diseases clinics with the complaints of spinal pain or fever which did not relieve by rest. Subsequently, contrast-enhanced MRI was ordered.

The classification of Modic et al. (1998), which is based on signal intensity changes in vertebral endplates, was used. Patients who had Modic changes type I (hypo intense signal in T1-weighted imaging and hyperintense signal in T2-weighted imaging) were noted down as MRI (+). Degenerative changes in discs were also evaluated using a grading system devised by Pfirrmann et al. (2001). The changes in the MRI signal intensity, disc structure, and disc height were considered. The signal and height changes in the affected vertebra and discs, cortical irregularities in the vertebral body endplates and concomitant degenerative changes were assessed. Moreover, pathological signal involvement in the vertebra and disc, pathological findings in the paravertebral soft tissue, and the epidural region were evaluated following intravenous (IV) contrast media administration.

The following laboratory tests were ordered for patients whose MRI revealed pathological findings: the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count, Brucella immunoglobulin (Ig) -M, Ig-G, Wright's seroagglutination test, and Coombs anti-Brucella test.

Patients with Wright's seroagglutination test titer  $\geq 1:160$ , and a Coombs test titer  $\geq 1:320$  (Colmenero et al., 1996) were included in the study. The positive results of

**Table 1.** Data on laboratory findings.

	<b>CRP</b> <b>(mg/dL)</b>	<b>ESR</b> <b>(mm/hours)</b>	<b>WBC</b> <b>(x10<sup>3</sup>/ul)</b>	<b>NEU</b> <b>(x10<sup>3</sup>/ul)</b>	<b>LYMPHO</b> <b>(x10<sup>3</sup>/ul)</b>	<b>PLT</b> <b>(x10<sup>3</sup>/ul)</b>
	(Mean±SD)	(Mean±SD)	(Mean±SD)	(Mean±SD)	(Mean±SD)	(Mean±SD)
Beforetreatment	54.87±52.51	65.37±32.45	7,679.10±3,620.26	4,729.10±2,747.80	2,054.55±7,84.94	307,909.10±126,956.30
	(Min-Max)	(Min-Max)	(Min-Max)	(Min-Max)	(Min-Max)	(Min-Max)
	14-186	24-117	2,100-16,400	8,90-11,800	8,80-32,00	101,000-565,000
	(Mean±SD)	(Mean±SD)	(Mean±SD)	(Mean±SD)	(Mean±SD)	(Mean±SD)
Aftertreatment	2.72±1.74	18.82±12.34	6,216.36±1,418.66	3,200.91±1,175.04	2,312.73±4,35.02	257,363.64±88,677.25
	(Min-Max)	(Min-Max)	(Min-Max)	(Min-Max)	(Min-Max)	(Min-Max)
	1.1-6.9	5-47	3,500-9,300	1,710-6,330	1,350-2,720	141,000-432,000

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, WBC: White blood cell, NEU: neutrophil, LYMPHO: lymphocyte, and PLT: platelet.

Brucella immunoglobulin IgM and IgG were also considered. The QuantIFERON-TB test and tuberculin skin test were performed for the differential diagnosis of tuberculosis. Furthermore, blood samples, tissue and abscess materials were taken for microbiological analyses.

### Search criteria

A comprehensive and systematic literature search of electronic databases, including the EMBASE, PubMed, and OVID was performed. Keywords used were as follows: "Osteomyelitis", "Vertebral osteomyelitis", "Spondylodiscitis", or "Brucellar Vertebral Osteomyelitis".

The headings and abstracts of all the experimental and clinical studies were reviewed. The full texts of the appropriate studies were retrieved according to the headings and abstracts, and then the decision of whether to include or exclude these studies was made after a comprehensive review. Letters to the editor, bibliographies, reviews, and meta-analyses were excluded from the study (Karaarslan et al., 2017; Topuk et al., 2017; Karaarslan et al.<sup>a</sup>, 2018).

Critical appraisal checklists were used to assess and analyze the quality of the studies. Following this assessment, a consensus was reached in the event of disagreement. The obtained data were summarized, and the findings were compiled in a clear and understandable manner using tables (Figure 1).

The present study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Akgunet al., 2018; Akyuva et al., 2018; Karaarslan et al.<sup>b</sup>, 2018).

### Statistical analyses

The statistical analyses were performed using Minitab (version 16.0) software. After a descriptive analysis of different variables, Kruskal Wallis test was performed.

Pearson correlation coefficient was used to compare rates between groups. The alpha significance value was accepted as  $P < 0.05$ . Descriptive statistics were presented as number or frequency (%) using *Microsoft Office Excel (2013)*.

## RESULTS

The mean age of patients ( $n=11$ ) included in the study was  $53.09 \pm 15.71$  years and 27.27% of them were female. Fever was present in 9.09% of female patients, while it was present in 18.18% of male patients at the time of the admission to the clinic. Low back pain and difficulty in walking were present in 18.18% of female patients. However, of the male patients, 45.45% were suffered from low back pain, and 27.27% had difficulty in walking.

The levels of involvement in female patients were as follows: Thoracic (T) 8-9, Lumbar (L) 5-Sacral (S) 1 and T10-11, while those in male patients were as follows: L3-4 ( $n=2$ ), L3-4/L4-5 double level, L4-5/L5-S1 double level ( $n=2$ ), L5-S1 ( $n=1$ ), and T12-L1 ( $n=2$ ).

One patient (Male, 37 years) was diagnosed with sacroiliitis along with T12-L1 involvement. Laboratory findings of patients were evaluated (Table 1).

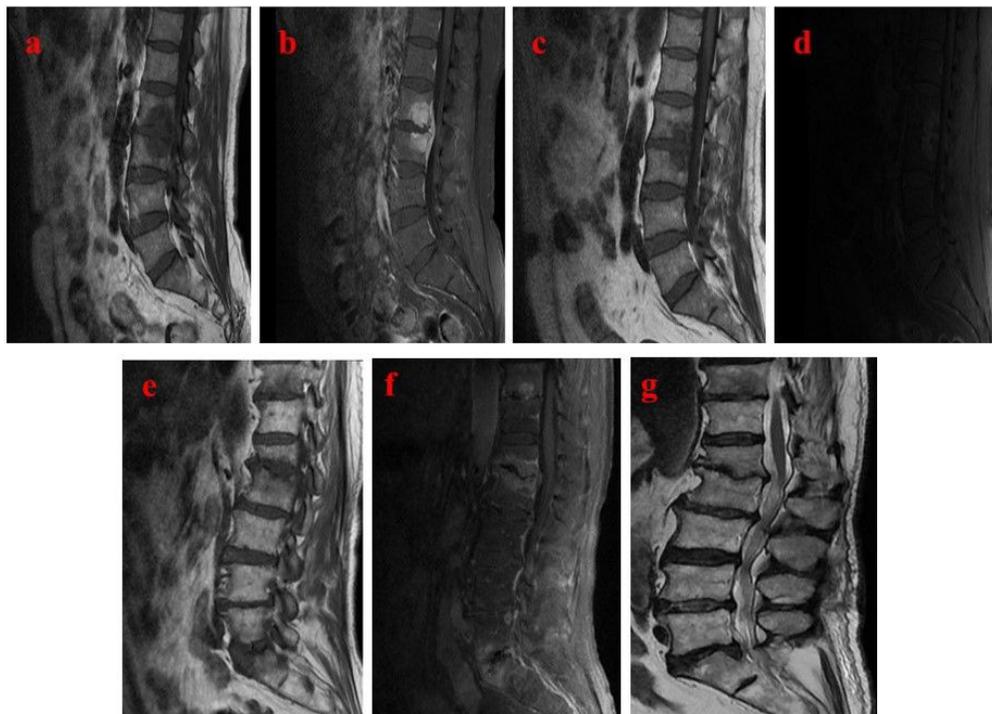
Post-treatment statistical significance was observed to be lower in CRP, ESR, WBC, NEU, LYMPHO, and PLT values as compared to that in pre-treatment ( $P < 0.05$ ).

The Rose Bengal test and Brucella-IgG were positive in all the patients. However, Brucella-IgM was negative in four patients, one of whom was female, and it was positive in the remaining seven patients.

Significant correlation was observed between CRP, ESR, WBC, NEU values and The Rose Bengal test and Brucella-IgG test result ( $p < 0.05$ ;  $r > 0.08$ ).

Nine patients were treated successfully with specific rifampicin (300 mg 1x2 for at least six weeks), streptomycin (1 g 1x1 intramuscular for three weeks) and doxycycline (100 mg 2x1 for at least six weeks).

The device used during radiological imaging was a 1.5



**Figure 2.** Demonstrative MRI of the two cases.

Tesla MRI scanner. The demonstrative data of one patient shown in Figure 2 were as follows: (a) Pre-medical treatment period; decreased signal intensity was observed in the vertebral corpus endplates adjacent to the L2-3 intervertebral disc in the sagittal T1-weighted fast spin-echo (FSE) sequence. Moreover, cortical bone irregularities and subcortical bone resorption were also detected. (b) Pre-medical treatment period; intense enhancement in the endplates adjacent to the L2-3 intervertebral disc, where hypo intense was present in the T1-weighted sequence, was observed in IV gadolinium chelate compound-administered patient in the sagittal T1-weighted FSE fat-suppressed (FS) sequence. Furthermore, concomitant minimal enhancement of the L2-3 disc and epidurals of tissue enhancement narrowing the spinal canal at the level of L2-3 intervertebral disc.

The following post-medical treatment observations were made in the sagittal T1-weighted FSE sequence: (c) The involvement of the endplates adjacent to the L2-3 intervertebral disc was observed to be reduced but not disappeared. The observations in the sagittal T1-weighted FSE FS sequence after contrast agent administration were as follows: (d) Decreased enhancement was observed in the endplates adjacent to the L2-3 intervertebral disc as compared to that in the pre-treatment period. Moreover, increased enhancement was interestingly monitored in the L2-3 intervertebral as compared to the pre-treatment period. More interestingly, the soft tissue enhancement in the anterior epidural

space was almost completely disappeared. There were two patients, who were unresponsive to medical treatment, with high CRP and ESR level as well as symptoms of deterioration.

The demonstrative MRI data of patients (1 Male; 1 Female) operated on due to the therapeutic failure were as follows: In pre-operative T1-weighted FSE sequence (e) Loss of signal intensity was observed in the endplates adjacent to L1-2 and L5-S1 intervertebral discs and the lower endplate of the T11 vertebra. Furthermore, the reduction in the height of the L1 vertebra seemed interesting. In pre-operative T1-weighted FSE-FS sequence: (f) There was an intense enhancement in the end plates adjacent to L1-2 and L5-S1 intervertebral discs, the lower endplate of T11 vertebra, and T11-12 intervertebral disc. And also epidural enhancement was observed at the level of L1-2 intervertebral disc.

Lumbar spinal stenosis and foraminal stenosis secondary to epidural enhancement were observed at L5-S1 level. Following clinical and neurological examination, the complaints of the patient were detected to be secondary to the pathology of L5-S1 level. The followings were observed in the post-operative, sagittal T2-weighted MRI of the patient: Hemilaminectomy (Right-L5 level) and foraminotomy (Right-S1 level) were performed, after this surgery, decompression of the lumbar spinal canal was achieved and compression on the right S1 nerve root was eliminated (Figure 2.g).

The decision of surgery was made due to the occurrence of the lumbar spinal stenosis and foraminal

**Table 2.** Summary of the outcomes of conservative, medical and surgical treatment modalities respectively.

Parameters	Frequency (%)
Conservative&Medicaltreatment	100
Failuretotreatment	18.18
Surgicaltreatment	18.18
Post operativefunctionalsequela	None
Death	None

stenosis. The patient was placed in a prone position under general anesthesia. Surgical site antisepsis was provided using batticon solution, then the sterilized site was covered. The surgical level was confirmed using C-arm scopy. Following a midline skin incision, the lumbar superficial fascia was incised, and a surgical microscope was used to visualize the operation site. Hemilaminectomy (Right-L5 level) and flavectomy were performed respectively. Fibrotic, fragile tissues were observed at the epidural space, then excised. Subsequently, foraminotomy (Right-S1 level) was performed and S1 nerve root was decompressed. The operation was terminated after achieving hemorrhage control. All patients who underwent surgery or received medical treatment were called for control at least once a month after termination of the treatment (Table 2).

## DISCUSSION

Many studies have reported that *Brucella melitensis* is the most commonly isolated species in brucellosis cases (Young, 2010). In the present study, *Brucella* species were not isolated. Diagnostic methods for brucellosis are primarily based on serological assays. Pharmacological agents used for the treatment of any *Brucella* species do not change, and drugs such as rifampicin, streptomycin, and doxycycline are administered to patients. Thus, the mentioned agents were given to patients in this study.

A study has reported that laboratory findings of such patients, especially those with focal complications, may reveal leucocytosis, leukopenia, thrombocytopenia, and anemia (Franco et al., 2007). A moderate or slight increase in ESR and CRP levels and a moderate increase in liver enzymes maybe observed (González-Gay et al., 1999; Franco et al., 2007).

The final diagnosis of Brucellosis is reported to be established through the bacteria isolated from samples such as blood, bone marrow, tissue and cerebrospinal fluid. Blood and bone marrow cultures are frequently positive during the acute phase. The Rose Bengal test is usually used as a screening test and the positive result of this test should be confirmed by a serum agglutination test (González-Gay et al., 1999; Franco et al., 2007).

Given the results reached in the mentioned studies (González-Gay et al., 1999; Franco et al., 2007), the

Rose Bengal test should not solely be used for the diagnosis of patients with a recent history of infection or brucellosis in regions where the disease is endemic.

As is well known antimicrobial agents should not be used carelessly. After the infection is diagnosed, the sensitivity of the isolated primary agent should be determined. A pathology-based treatment may not be appropriate in every case.

One of the broad-spectrum antibiotics should be prescribed when the pathogenic agent is not isolated, or its isolation and identification take a too long time. Once the sensitivity of the agent is determined, either the use of the same antibiotic is continued, or another suitable antimicrobial agent can be prescribed. One of the two main criteria for determining the *in-vitro* activity of antibacterial drugs is the minimal inhibitory concentration (MIC) value. The MIC represents the lowest concentration of a drug which prevents the growth of the causative pathogen. That's to say, the concentration of the drug that kills the agent should be greater than the inhibitor concentration. The conventional antibiotic discs cannot provide satisfactory outcomes in adjusting the dosage of antibiotics used for the treatment of BVO. The calculation of the MIC values is important for almost all microorganisms since high concentrations can be achieved through antibiotic treatment.

In the present study, the antibiotics were orally and intramuscularly administered. No data concerning whether antibiotics were administered after the MIC values for microorganisms had been calculated were found in the medical records of the patients.

The normal biochemical parameters have been reported to be of slight importance in the diagnosis of BVO. However, leucocytosis, neutrophilia and the presence of high ESR and CRP levels have been reported to provide more diagnostic support (Dogan et al., 2019). In the present study, leucocytosis, neutrophilia, and high ESR and CRP levels were considered.

A study has reported that MRI is more efficient in visualizing soft tissue and bone marrow as compared to direct radiography and computed tomography (Gross et al., 2002; Walenkamp, 1997). However, it has also reported that MRI may be less sensitivity than other modalities for the detection of cortical osseous tissue abnormalities, and that MRI may not always be appropriate to detect the changes in the late bone tissue, such as sclerosis, while it is insensitive for the detection of

the bone marrow edema in the early stage of osteomyelitis. In that study (Gross et al., 2002; Walenkamp, 1997), the analyses performed using contrast agents such as gadolinium have been proposed to be able to provide reliable data in the identification of abscess formation. In addition, MRI can be used safely in a pre-operation planning period to obtain a view about the surrounding soft tissues (Manelfe, 1991).

Some studies have suggested that MRI, a sensitive and specific diagnostic method, may help clinicians to diagnose BVO (Karaarslan et al.<sup>c</sup>, 2018; Sharif HS, 1992). Furthermore, MRI has been reported to be the most reliable method to diagnose spondylodiscitis, due to its high sensitivity (96%), high specificity (94%), and capacity to provide elaborate data on paraspinal tissues and the epidural space (Lener et al., 2018). In the present study, the hypothesis that MRI is helpful in the diagnosis of spondylodiscitis due to its high sensitivity, and high specificity was confirmed.

Osenbach et al. (1990) investigated BVO cases along with the pyogenic vertebral osteomyelitis. Cordero et al. reported that the clinical course and prognosis of BVO significantly differed from those of tuberculosis VO, and pyogenic vertebral osteomyelitis (Cordero et al., 1991).

In a study by Perrone et al. (1994), surgical management rate of disease was 45%, while that in the present study was only 18.18%. Patzakis et al. (1991) reported the presence of severe functional sequelae in 10% to 25% of the cases, while no patient with severe functional sequelae was observed in this study. Given the data obtained, the rate of mortality and relapse was observed not to be similar to those reported in previous studies.

In recent years, systematic reviews and meta-analyses have increasingly been accepted for publication by life sciences journals (Akgun et al., 2018; Akyuva et al., 2018; Karaarslan et al., 2017). Such studies provide all available data on a matter of interest as compared to the conventional reviews, thus, they are significantly helpful for researchers (Topuk et al., 2017; Karaarslan et al.<sup>a</sup>, 2018; Karaarslan et al.<sup>b</sup>, 2018). Therefore, it is necessary to rigorously compile the findings of the previous studies, considering the quality of the mentioned studies (Akgun et al., 2018; Akyuva et al., 2018; Karaarslan et al., 2017; Topuk et al., 2017; Karaarslan et al.<sup>a</sup>, 2018; Karaarslan et al.<sup>b</sup>, 2018).

In this study, it was planned to use "fixed effects" or "random effects" models to evaluate the heterogeneity between studies. Hence, different assumptions could be made about all the obtained results after the evaluation of the data.

The aim was initially to collect the data obtained from the studies on the diagnosis and treatment of BVO, then to compile the findings extracted from the collected data to make an overall assessment. However, a meta-analysis including a mathematical combination of clinical results extracted from the source data could not be performed,

since there was not any common knowledge. Therefore, the data included were presented as a systematic review. The first limitation of this study is that it had a retrospective design. The second limitation is that the possibility that the mistakes made when classifying the data obtained from the articles included in the study were missed by the authors.

In conclusion, the samples should be evaluated carefully when establishing a final diagnosis of Brucellosis. It is not possible to make a differential diagnosis for BVO through diagnostic imaging. Not only the structures of the vertebral tissue but also the content of the disc tissue should be evaluated for osteomyelitis using appropriate classifications. It should be kept in mind that the Rose Bengal test is a screening test, and that positive test results should be confirmed using a serum agglutination test. It should not be forgotten that the conventional antibiotic discs cannot provide satisfactory outcomes in adjusting the dosage of antibiotics used for the treatment of BVO. It is important to determine the antibiotic doses and duration after the MIC values for microorganisms are calculated in patients who are planned to be treated with local antibiotics.

## CONCLUSION

A multidisciplinary approach is important for conservative, medical and surgical treatments of patients diagnosed with BVO. Both microbiological and radiological findings should be evaluated by experts to make a diagnosis. After making an accurate diagnosis, the treatment modality should be determined by a committee including a neurosurgeon, infectious disease specialist, and medical pharmacologist. After selecting the appropriate antimicrobial therapy for BVO, the appropriate dose and duration should be determined. Surgical treatment should be provided immediately when treatment cannot be achieved through medical treatment. Indication for surgical treatment should be established after detailed clinical, and radiological assessments are performed. Surgical intervention should be performed if necessary. Thus, complication and chronicity can be prevented, and the severity and duration of the disease can be shortened.

## DECLARATIONS

### Competing interests

The authors declare that they have no competing interest.

**Financial Disclosure:** There are no financial supports.

## REFERENCES

- <sup>a</sup>Karaarslan N, Yilmaz I, Akgun FS, Caliskan T, Ozbek H, Ates O (2018). Systematic Evaluation of Desmopressin Applied to the Patients with Aneurysmal Subarachnoid Haemorrhage in the light of the Literature. *Turk Neurosurg*; Apr 9. doi: 10.5137/1019-5149.JTN.23064-18.1. [Epub ahead of print].
- Akgun FS, Karaarslan N, Yilmaz I, Ozbek H, Caliskan T, Ates O (2018). Systematic Evaluation of Adverse Reactions That May Occur After Injection of Type-A Botulinum Toxin in Patients with Spasmodic Torticollis Admitted to Emergency Department. *Merit Res. J. Med. Me. Sci.* 6(2): 68-72.
- Akyuva Y, Karaarslan N, Yilmaz I, Caliskan T, Sirin DY (2018). Will intervertebral disc diseases be prevented by siRNA or miRNA-based genomic treatment modalities? *Merit Res. J. Med. Me. Sci.* 6(1):6-15.
- Ariza J, Gudiol F, Valverde J, Pallarés R, Fernández-Viladrich P, Rufi G, Espadaler L, Fernández-Nogues F (1985). Brucellar spondylitis: a detailed analysis based on current findings. *Rev Infect Dis*; 7(5): 656-64.
- Bianchini S, Esposito A, Principi N, Esposito S (2018). Spondylodiscitis in Paediatric Patients: The Importance of Early Diagnosis and Prolonged Therapy. *Int J Environ Res. Public Health*; 15(6): E1195.
- <sup>b</sup>Karaarslan N, Yilmaz I, Ozbek H, Caliskan T, Topuk S, Sirin DY, Ates O (2018). Systematic Evaluation of Promising Clinical Trials- Gene Silencing for the Treatment of Glioblastoma. *Turk. Neurosurg*; Apr 6. doi: 10.5137/1019-5149.JTN.22467-18.3. [Epub ahead of print].
- <sup>c</sup>Karaarslan N, Yilmaz I, Ozbek H, Oznam K, Ates O, Erdem I (2018). Is Implant Washing and Wound Irrigation with Rifampicin Effective for Preventing Surgical Site Infections in Lumbar Instrumentation? *Turk Neurosurg*; 28(6): 904-9.
- Colmenero JD, Jiménez-Mejías ME, Sánchez-Lora FJ, Reguera JM, Palomino-Nicás J, Martos F, García de las Heras J, Pachón J (1997). Pyogenic, tuberculous, and brucellar vertebral osteomyelitis: a descriptive and comparative study of 219 cases. *Ann Rheum Dis*; 56(12):709-15.
- Colmenero JD, Reguera JM, Martos F, Sanchez-Mora D, Delgado M, Causse M, et al (1996). Complications associated with Brucella melitensis infection: a study of 530 cases. *Medicine (Baltimore)*; 75:195-209.
- Cordero M, Sánchez I (1991). Brucellar and tuberculous spondylitis. A comparative study of their clinical features. *J Bone Joint Surg Br*; 73B:100-3.
- Dogan M, Simsek AT, Yilmaz I, Karaarslan N (2019). Evaluation of Empirical Antibiotic Treatment in Culture-Negative Pyogenic Vertebral Osteomyelitis. *Turk Neurosurg*; Jan 02, 2019, DOI: 10.5137/1019-5149.JTN.25018-18.2.
- Eren Gok S, Kaptanoglu E, Celikbas A, Ergonul O, Baykam N, Eroglu M, Dokuzoguz B (2014). Vertebral osteomyelitis: clinical features and diagnosis. *Clin. Microbiol. Infect*; 20(10):1055-60.
- Esmailnejad-Ganji SM, Esmailnejad-Ganji SMR (2019). Osteoarticular manifestations of human brucellosis: A review. *World J Orthop*; 10(2):54-62.
- Franco MP, Mulder M, Gilman RH, Smits HL (2007). Human brucellosis. *Lancet Infect Dis*; 7(12): 775-86.
- González-Gay MA, García-Porrúa C, Ibañez D, García-País MJ (1999). Osteoarticular complications of brucellosis in an Atlantic area of Spain. *J Rheumatol*; 26(1):141-5.
- Gross T, Kaim AH, Reggazoni P, Widmer AF (2002). Current concepts in posttraumatic osteomyelitis: a diagnostic challenge with new imaging options. *J Trauma*; 52:1210-9.
- Kamiya N, Hatakeyama S, Kanda N, Yonaha S, Akine D, Yamamoto Y, Matsumura M (2018). Significance of repeat magnetic resonance imaging in diagnosing vertebral osteomyelitis. *J Gen Fam Med*; 20(2):68-71.
- Karaarslan N, Kaya YE, Yilmaz I, Ozbek H, Bilir EB, Kaplan N, Sirin DY, Akyuva Y, Gurbuz MS, Oznam K, Akkaya S, Mutlu CA, Guler O, Ates O, Mahiroglu M (2017). Will it be possible to prevent lumbar degenerative disc diseases in the future by means of vitamin D receptor gene manipulation? *Merit Res. J. Med. Me. Sci.* 5(10): 500-10.
- Lener S, Hartmann S, Barbagallo GMV, Certo F, Thomé C, Tschugg A (2018). Management of spinal infection: a review of the literature. *Acta Neurochir (Wien)*; 160(3): 487-96.
- Manelfe C (1991). Imaging of the spine and spinal cord. *Curr Opin Radiol*; 3(1):5-15.
- Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR (1998). Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. *Radiology*; 166:193-9.
- Osenbach RK, Hitchon PW, Menezes AH (1990). Diagnosis and management of pyogenic vertebral osteomyelitis in adults. *Surg Neurol*; 33:266-75.
- Patzakis MJ, Rao S, Wilkins J, Moore TM, Harvey PJ (1991). Analysis of 61 cases of vertebral osteomyelitis. *Clin Orthop*; 264:178-83.
- Perronne C, Saba J, Behloul Z, Salmon-Ceron D, Lepout C, Vilde JL, Kahn MF (1994). Pyogenic and tuberculous spondylodiskitis (vertebral osteomyelitis) in 80 adult patients. *Clin Infect Dis*; 19:746-50.
- Pfirrmann CW, Metzdorf A, Zanetti M, Hodler J, Boos N (2001). Magnetic resonance classification of lumbar intervertebral disc degeneration. *Spine*; 26(17):1873-8.
- Sharif HS (1992). Role of MR imaging in the management of spinal infections. *AJR Am J Roentgenol*; 158 (6):1333-45.
- Singh DK, Singh N, Das PK, Malviya D (2018). Management of Postoperative Discitis: A Review of 31 Patients. *Asian J Neurosurg*; 13(3): 703-6.
- von der Hoeh NH, Voelker A, Hofmann A, Zajonz D, Spiegl UA, Jarvers JS, Heyde CE (2018). Pyogenic Spondylodiscitis of the Thoracic Spine: Outcome of 1-Stage Posterior Versus 2-Stage Posterior and Anterior Spinal Reconstruction in Adults. *World Neurosurg*; 120:e297-e303.
- Walenkamp GH (1997). Chronic osteomyelitis. *Acta Orthop Scand*; 68:497-506.
- Young EJ (2010). Brucella species. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*. 7th ed. Philadelphia: Churchill Livingstone; 2921-5.